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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
ENEWOLD, J	
ART UNIT	**PAPER NUMBER**
1655	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/228,639	WESTON ET AL.	
	Examiner	Art Unit	
	Jeanine A Enewold	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *08 May 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

1. Currently claims 1-3, 5, 10-16 are pending. While Amendment B, filed May 2000, added Claims 11-15, a Claim 11 was already pending in the application. Claim 11 was entered by amendment A into the instant application on January 12, 1999. Thus, the added claims have been renumbered as 12-16.

Priority

2. This application claims priority to a Great Britain foreign document 9800536.6, filed January 13, 1998. The instant claims appear to be enabled by the disclose of the foreign document.

Sequence Rules

3. Claim 11 is directed to nucleotides which are longer than 10 nucleotides in length and thus are subject to the sequence rules which require the sequence to be identified by SEQ ID NO:s. It appears that these sequences are SEQ ID NO: 1-4 respectively. Appropriate correction is requested.

Drawings

4. The drawings are objected by the draftsman (see PTO 948).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-2, 10-13, 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-2, 10-11, 16 are indefinite because as written it is unclear whether the two separate reaction vessels containing genomic DNA from a patient are contacted with both primer sets of A and B or whether one contain is contacted with primer set A and the other contain is contacted with primer set B. While the claim does state "respectively" this does not help to clarify the matter.

B) Claims 13 and 15 are rejected as indefinite because two distinct sequences have been identified as SEQ ID NO: 24. Neither of these sequences appears to be the SEQ ID NO: 24 identified in the computer printout of the disk. It does appear that the two sequences that are named SEQ ID NO:24 are collectively SEQ ID NO: 4. Thus, correction is requested.

C) Claims 2, 16 are indefinite over the recitation "wherein on or more diagnostic primers is used with one or more amplification primers in one or more cycles of PCR amplification" because it is unclear how diagnostic primers differ from amplification primers. It is presumed that all primers amplify under some condition. Thus, the metes and bounds of the instant claims are unclear.

D) Claims 3, 5, 12, 13, 16 are indefinite over the recitation "a set of allele specific primers" in claims 3 and 5 and "diagnostic primer sequences" in claims 12 and 13 because while Claims 12 and 13 are intended to limit Claims 3 and 5, it is unclear what

is the difference between allele specific and diagnostic primers. Further, Claims 12 and 13 are indefinite because it is unclear whether the set of primers contains a set of allele specific primes and the recited diagnostic primers. For example, 6 allele specific primers and the 6 diagnostic primers recited, or whether the 6 diagnostic primers may be the same as the 6 allele specific primers.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-3, 5, 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al (EPO 497527A1, August 5, 1992) and Ferrie et al (Am. J. Human Genetic, Vol. 51, pg. 251-262, 1992) in view of Estivill et al (Human Mutation, Vol. 10, pg. 135-154, 1997) and CFGAC (Cystic Fibrosis Genetic Analysis Consortium, Human Mutation, Vol 4, pg. 167-177, 1994)

Little et al. (herein referred to as Little) teaches a method for detecting single nucleotide variations in the cystic fibrosis gene by amplification refractory mutation system (ARMS). The ARMS method includes treating the sample with nucleoside triphosphates, an agent for polymerization and a diagnostic primer. Moreover, Little teaches that ARMS is able to selectively amplify multiple sites to obtain multiple amplification products to be distinguished simply, accurately, and with minimal operator

skill thus providing a robust technique for screening a single sample for multiple nucleotide variations (pg. 2, lines 47-50). Little teaches numerous primers for ARMS analysis of the cystic fibrosis gene (pg. 27-29). Primers for 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H mutations are provided. The instant primers of SEQ ID NO: 12, 16, 17, 18 are identical to the Little primers 1879, 1880, 1879, 2072, respectively. Little teaches an ARMS reaction in which G542X, F508(M), 621+1 G>A, G551D mutations are multiplexed and analyzed.

Ferrie et al. (herein referred to as Ferrie) teaches the development of a multiplex ARMS test for common mutations in the CFTR gene. Ferrie teaches that ARMS systems have numerous advantages over other PCR-based systems including rapid, reliable, nonisotopic, and easily obtained results (pg. 251-252). Ferrie teaches that in principle, ARMS tests can be developed for any mutation. Ferrie teaches that ARMS tests have been developed for the following CFTR mutations: 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H. Moreover, Ferrie teaches how to increase sensitivity and design an ARMS system which would provide the ordinary artisan with the tools needed to optimize a reaction for a specific need. Ferrie teaches altering the primer sequence has a large effect on the yield and specificity of an individuals reaction within the multiplex, while small changes were obtained by altering the primer concentrations (pg. 258, col. 1). Further, Ferrie teaches that the yield of the primer pair was affected by the rate of hybridization of ARMS primer to the target DNA and the rate at which the bases at the 3' end of the AMRS primer form a suitable substrate for Taq DNA polymerases (pg. 259, col. 2). Modification of the

3' sequence can change the specificity without significantly altering the calculated melting temperature (pg. 259, col. 2). Specificity may also be obtained by additional stabilization in which the choice of mismatched based was determined experimentally, given that purine/purine mismatches or pyrimidine/pyrimidine mismatches showed greater destabilization (pg. 259, col. 2). Also, specificity may be obtained by reducing the primer concentration and inclusion of control PCR reactions (pg. 259, col. 2). Ferrie also cites other references which discuss improving specificity by reducing the concentration of dNTP in the reaction (pg. 259, col. 2). Long primers (30 mers) ensured false priming events were minimized and that primer template interactions were stabilized and minimizing the disruptive effect of DNA polymorphisms (pg. 260, col. 1). Yields of the reaction needed to be relatively similar. Finally, ARMS multiplex has proved extremely reliable and has made the greatest impact on the speed of delivery of results (pg. 260, col. 2).

Neither Little nor Ferrie specifically teach the combination of primers for all of the recited mutations.

However, Estivill et al. (herein referred to as Estivill) teaches geographic distribution and regional origin of 272 cystic fibrosis mutations in European populations. There mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. G542X, W1282X, N1303K, F508(M), G551D are taught to be the most common mutations. Furthermore, all of 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T,

621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations are common in more than one region (Table 2 and 3).

Furthermore, CGFAC teaches that 24 of the most common mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. The specific frequencies in which these mutations are found are provided.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Little, Ferrie in view of Estivill and CGFAC to obtain the invention as a whole. Little teaches primers for ARMS reactions to determine mutations in the CTFR gene. Ferrie teaches the modifications needed to be made to perform ARMS multiplex analysis. The ordinary artisan would have been able to have performed routine experimentation to optimize the ARMS systems desired for the particular situation. Further, all of the claimed mutations were known at the time the invention were made, as exemplified by Estivill and CFGAC. Further Estivill and CFGAC taught the relative frequencies of the mutations in numerous populations. Thus, the ordinary artisan would have been motivated to either have selected certain mutations to screen for which were more probable in the specific individual being studied. Or, the ordinary artisan would have been motivated to screen for a more generic set of mutations which were relatively probable in all different populations based upon the teachings of Little and Ferrie in view of Estivill and CFGAC. Thus, based upon the general knowledge at the time the invention was made, the ordinary artisan would have been motivated to have made the invention as a whole.

Since Estivill and CFGAC provides the frequencies of CFTR mutations, Ferrie teaches the ordinary artisan how to optimize multiplex ARMS reactions, and Little teaches ARMS reactions are appropriate for determining single mutations in the CFTR, it would have been obvious to have designed a multiplex reaction which suited the individual needs of the artisan as all such modification would have produced functional equivalent results based upon the teachings of Little and Ferrie.

Further, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Little with the teachings of Ferrie. Also, since the sequence of the CFTR gene was known, mutations within the CFTR were known, as taught by Estivill and CFGAC, generating primers for these regions would have been obvious over the teachings of Little and Ferrie which teach the properties of the primers needed for the ARMS assay. The ordinary artisan would have been motivated to determine whether the mutation was present in a sample using the multiplex ARMS method of Ferrie since the ARMS method is rapid, reliable and nonisotopic. The ordinary artisan would have further been motivated to have optimized primer selection to obtain optimal results for the ARMS reaction, based upon the teachings of Ferrie. Further, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For

example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologues of the full length disclosed nucleic acid sequence of the CFTR gene concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited reference in the absence of secondary considerations.

Conclusion

7. **No claims allowable over the art.**

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Fortina et al (Human Genetics, Vol. 90, pg. 375-378, 1992)- teaches detecting common mutations in the CFTR gene with multiplex allele-specific polymerase chain reaction.

B) Scobie et al (Molecular Human Reproduction, Vol. 2, No. 3, pg. 203-207, March 1996)- teaches ARMS reactions for detecting CF mutations.

C) Sereth et al (Human Genetics, Vol. 92, pg. 289-295, 1993)- teaches mutations in the CFTR gene and provides the most common mutations.

D) Newton et al (Nucleic Acids Research, Vol. 17, No. 7 pg. 2503-2516, 1989)- teaches ARMS.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold
June 6, 2000

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600